REMARKS/ARGUMENTS

Claims 32, 33, 36-39, 41, 43, 44, 47, 49 and 50 have been amended to more fully claim the disclosed invention. New claim 52 is introduced into the application. No new matter has been added. The additional fee for an additional dependent claim is enclosed. Early examination and favorable consideration of the above-identified application is earnestly solicited.

Claims 32 to 51 were rejected under 35 U.S.C. 103(a) based on the combination of Frangin and Poss. Applicants respectfully disagree with the foregoing rejection of the claims; and reiterate and reassert the arguments previously made with regard to distinguishing the subject matter of the present invention, as recited in the claims, from those references.

Frangin discloses the use of certain benzofuran derivative compounds, particularly amiodarone, dronedarone, and desethylamiodarone, and their salts, having antiarrhythmic activity, for the treatment of cardiovascular disease. The use of these compounds, together with a pharmaceutically acceptable vehicle is disclosed (see, e.g., col. 6, lines 50-61) and claimed (see, e.g., claim 1). In certain specific alternative embodiments of Frangin, the further simultaneous or sequential administration of an additional cardioactive agent is disclosed (see, e.g., col. 8, line 34 - col. 9, line 38) and claimed (see, e.g., claims 23 - 25). Frangin also discloses, at col. 6, lines 24 - 28 (which occurs before the further disclosure of the embodiment having a further, second active agent associated with the principal benzofuran derivative agent) that the "pharmaceutical compositions" (again apparently referring to the benzofuran derivatives, i.e., the principal active ingredient, referred to in the preceding paragraph at col. 6, lines 21 - 23) may be provided in any form (with "transdermal" being mentioned; see col. 6, line 27) for administration to humans. In the paragraph ending at col. 6, lines 33 - 36, reference is made to an administerable unit (again, understood to mean of the principal active agent, i.e., benzofuran derivative) including a device called a "patch" for transdermal administration.

It is only subsequently, at col. 8, lines 66 - 67, in the discussion of administration of the principal benzofuran derivative agent simultaneously or sequentially associated with at least one additional cardioactive agent, that angiotensin II inhibitors are mentioned.

While Frangin contains an extensive discussion of clinical data, those clinical trials used tablets. The only formulations exemplified in Frangin are tablets, gelatin capsules, and an injectable solution. See col. 7 of Frangin.

It is respectfully submitted that Frangin does not provide enabling disclosure to teach administration of even the principal active agent (benzofuran derivative) via a transdermal "patch" delivery system in that it does not provide enabling disclosure as to the type and construction of such a patch that could be utilized for the delivery of the benzofuran derivative.

According to an interpretation most favorable to Frangin, the appropriate "pharmaceutically acceptable vehicle" for the transdermal route, meaning via a "patch" type device, rather than via a topical cream or ointment, might be thought to include the "patch" itself or the materials out of which a "patch" were constructed. Although the list of appropriate pharmaceutical excipients or vehicles recited at col. 6, lines 58 - 61, is only exemplary, that listing does not include a transdermal patch per se or materials from which same would be constructed, but rather only includes compounds and substances typically associated with other delivery routes, e.g., oral, parenteral, sublingual, and topical. Applicants respectfully submit that Frangin does not teach, disclose, or suggest that candesartan is capable of delivery by a transdermal "patch".

Poss discloses certain indole and benzimidazole-substituted quinoline derivatives, which are angiotensin II inhibitors; and that the disclosed compounds are capable of administration by transdermal patches (see col. 8, lines 19 - 23). Poss does not disclose or even mention candesartan, which although an angiotensin II inhibitor, is not, in any case, one of the class of indole and benzimidazole-substituted quinoline derivative compounds disclosed by Poss. Therefore, there is nothing in Poss that teaches, discloses, or even remotely suggests that candesartan is capable of delivery by a transdermal "patch" type delivery mechanism or

route. A person of ordinary skill in the art would recognize that although candesartan is an angiotensin II inhibitor, it has a different structural formula and properties from the compounds of Poss, so that just because Poss states that the compounds it discloses are capable of administration by a transdermal "patch", that does not mean that all angiotensin II inhibitors, especially those with different structures and properties, such as candesartan, are similarly capable of delivery by that route. In fact, applicants state in the present application at page 3, lines 9 - 13, that "it has now been found, **surprisingly** [emphasis supplied], that candesartan and/or its pharmaceutically suitable esters and salts can be administered by means of a transdermal therapeutic system in such a way that a therapeutically effective blood level is reached", thereby indicating that according to the prior art, it was thought that candesartan was incapable of being effectively delivered by a transdermal route.

Accordingly, it is respectfully submitted that the 35 U.S.C. 103 (a) rejection of claims of the present application as being obvious over Poss in view of Frangin is inappropriate and should be withdrawn; and it is further respectfully submitted that the now pending claims, patentably distinguish over Poss, either taken alone or in the Examiner's proffered combination with Frangin.

Claims 32 to 51 have been rejected under 35 U.S.C. 103(a) as unpatentable over Poss and Frangin in view of U.S. Patent No. 5,464,628 to Jalonen et al. ("Jalonen"). Likewise, this rejection is improper and the pending claims define patentable subject matter over this combination of references.

The Poss and Frangin references have been discussed above and those comments should be considered as if repeated here at length.

Jalonen discloses certain pharmaceutical compositions containing 4-substituted imidazoles, that are capable of being administered transdermally, which, according to the reference, includes in the form of an ointment, emulsion, gel, lotion, solution or cream (i.e., what is generally referred to as "topically", and what is thought to be encompassed by the use of the term "topical" in Frangin, discussed above); as well as by one of the three delivery systems (i.e., "patch" type systems) disclosed in Jalonen.

As with Poss, discussed above, Jalonen does not disclose or even mention candesartan, which, in any case, is not one of the class of 4-substituted imidazole compounds disclosed by Jalonen. Candesartan, as disclosed in the specification of the present application at page 1, second paragraph, is (2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid). The structural formula of candesartan is illustrated in the prior submission. As can be seen, the structure of candesartan is different from the structure of the compounds in Jalonen, as shown by formulae I and II of that reference. Candesartan a carboxylic acid-substituted benzyl group attached to the imidazole group, which is not present in the compounds of Jalonen. Therefore, there is nothing in Jalonen that teaches, discloses, or even remotely suggests that candesartan is capable of delivery by a transdermal "patch" type delivery mechanism or route. The compounds of Jalonen are disclosed to be α_2 - adrenoceptor active agents, not angiotensin II inhibitors, although certain particular substituted compounds of the formulae disclosed in Jalonen are said to have, *inter alia*, antihypertensive effects (see, e.g., col. 1, lines 36-66). A person of ordinary skill in the art would recognize from the fact that because candesartan has a different structural formula and properties from the compounds of Jalonen, just because Jalonen states that the compounds it discloses are capable of administration by a transdermal "patch", that does not mean that all compounds having antihypertensive effects, nor even all imidazoles, especially those with different structure and properties, such as candesartan (with, at least, its additional carboxylic acid-substituted benzyl group, which affects its molecular weight, its stereochemistry, and hence its transdermal absorbability), are similarly capable of delivery by that route. It is again emphasized to the Examiner that applicants state in the present application at page 3, lines 9 - 13, that "it has now been found, **surprisingly** [emphasis supplied], that candesartan and/or its pharmaceutically suitable esters and salts can be administered by means of a transdermal therapeutic system in such a way that a therapeutically effective blood level is reached", thereby indicating that according to the prior art, it was thought that candesartan was incapable of being effectively delivered by a transdermal route. The differences in structural formula between the ester of candesartan (candesartan cilexetil) and the compounds of the structural formulae I and II of

Jalonen is seen from the previously submitted sheet showing the structural formula of candesartan cilexetil, also obtained from the website of Tianyu Pharmaceutical & Chemical Co., Ltd.

Further, Jalonen acknowledges that not all therapeutically active substances are suitable for transdermal administration at column 2, starting at lines 13 to 29 which reads as follows:

> Only a minor part of commercially available therapeutically active substances is suitable for transdermal administration due to many different pharmacokinetic and pharmacological reasons. One of the most limiting factors is, however, the physiocochemical properties of the therapeutically active substance itself. For a compound to be able to penetrate the skin it must have both lipophilic (fat soluble)and hydrophilic (water soluble) properties in a suitable proportion. Such a suitable ratio between the lipophilic and hydrophilic properties is not very common for drug substances. The ability of a drug to penetrate through the skin can be predicted by its partition coefficient P in octanol/water. It is known that compounds having an optimal partition coefficient penetrate the skin better than compounds with either higher or lower partition coefficients. This optimal partition coefficient value is different for different kinds of compounds.

Accordingly, any broad conclusion of obviousness is not warranted and the art specifically teaches away from such a broad conclusion.

It is submitted that the combination of references is improper. The rejections fail to set forth any motivation for the combination of references. It is clear that the rejections are based on hindsight reconstruction of one or more of the references wherein a reference has been edited or only a minor part of the reference has been considered. As acknowledged by Jalonen, not all therapeutically active substances are suitable for transdermal administration. Therefore, a passing mention, such as in Frangin, of transdermal administration without support by examples showing an operative embodiment cannot be relied upon either for purposes of anticipation or for purposes of obviousness. The mere fact that there is mention in the art of one or more features of the invention does not justify a combination of the references. See *In re Grabiak* 226 U.S.P.Q. 870 (Fed. Cir. 1985).

Accordingly, it is respectfully submitted that the 35 U.S.C. 103 (a) rejection of claims of the present application as being obvious over Poss and Frangin, in view of Jalonen, is inappropriate and should be withdrawn; and it is further respectfully submitted that the now pending claims, patentably distinguish over Jalonen, either taken alone or in the Examiner's proffered combination with Poss and Frangin, or with either of those individually.

It is submitted that the Examiner's response to the previously submitted arguments does not address the previously submitted arguments.

The quotation from the Keller and Merck decision is not appropriate. Applicants have addressed the combination and have addressed the propriety of the combination of references. The Examiner has not addressed the question of lack of enablement or lack of suggestion or motivation in the references. It appears the Examiner is equating a "mention" of a possibility as a "teaching". However, the two are not the same and even if they were, the combination is still improper. See *Grabiak*, supra.

Further, the Examiner has, by her comments, effectively, but impermissibly, supplemented the Frangin disclosure. The disclosure of Frangin does not invite mere routine optimization. To arrive at the present invention, based on Frangin's disclosure, with or without Poss and Jalonen, would require an extensive research project.

The Examiner's comments regarding the Jalonen reference highlights that an improper standard has been applied in formulating the obviousness rejection. Obviously, the Examiner is disregarding the fact that Jalonen teaches away from any broad conclusion of obviousness.

The decision of *In re Keller* cited the Examiner in two instances is inappropriate. The *Keller* decision issued before the creation of the Federal Circuit Court of Appeals. The Keller court's analysis for the test of obviousness fails to address questions of motivation. As discussed above, the Examiner has not shown motivation to combine the references.

It is submitted that at best the Examiner may have established "obviousness to try" but that is not the standard under 35 U.S.C. 103. See, *In re Geiger*, 2 U.S.P.Q. 2d 1276, 1278 (Fed. Cir. 1987).

In view of the foregoing, reconsideration and allowance of the application with claims 32 to 52 are earnestly solicited.

A check in the amount of $18.00 is enclosed for one extra dependent claim.

It is believed that no fees or charges are required at this time in connection with the present application; however, if any fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,
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